

Editorial: Immunosuppressive treatment for uveitis

In the majority of cases of endogenous uveitis there is little evidence that the disease is the result of proliferation of organisms in the ocular tissues. It is likely, however, that the inflammatory reaction is a response of the host to a foreign antigen, which could be an infective agent or a tissue constituent which has become altered by the disease process so that it acts as a foreign antigen. Antigen-antibody reactions are accompanied by the release of biologically active compounds which are responsible for local vasodilatation and increased permeability of blood vessels with exudation of serum proteins and the accumulation of white blood cells. In organs such as the skin the consequent redness and swelling do not cause undue tissue destruction, but when the eye is the battlefield these energetic responses may cause more damage than the initiating pathological process.

In these circumstances, as with tissue transplantation, it is advantageous to moderate the immune response. The label 'immunosuppressives' has been applied to drugs which do this, but it must be realized that the same drugs are labelled 'cytotoxic' when used in cancer therapy, and such immunosuppressive action as they have depends on their ability to destroy rapidly-dividing cells—whether viral, bacterial, or human. Cytosine arabinoside, for example, is a cytotoxic agent when used in the treatment of cancer but it also has immunosuppressive properties, and in addition it has an antiviral effect in herpes zoster and smallpox. We cannot be sure therefore whether the favourable results of treatment in diseases of obscure aetiology such as uveitis are due entirely to immunosuppression, and it is possible that the antibiotic properties of such drugs play a part.

Although not classed as immunosuppressive drugs, corticosteroids do suppress immune reactions and by their anti-inflammatory action reduce the damaging effects of the inflammatory response and remain the first line of defence in the treatment of uveitis. An acute attack of uveitis will almost always respond to adequate doses of corticosteroids, given either locally or systemically. It is in chronic cases requiring the long-term systemic use of high doses of steroids that problems arise from undesirable side-effects. The increase in weight, mental depression, and acneiform skin eruptions are unpleasant enough, but the more severe effects such as peptic ulceration, diabetes mellitus, osteoporosis, muscular wasting, and massive infection can threaten life. If other means of treatment

are effective in suppressing the inflammatory reaction and do not produce more severe side-effects, their use can be justified.

There are three main types of immunosuppressive drug: the nitrogen mustards, the antifolates, and the antipurines. The nitrogen mustards, which include chlorambucil and cyclophosphamide, are anti-mitotics which denature nucleoproteins by introducing an alkyl group into their molecule. The antifolates, such as methotrexate, block the enzyme dihydrofolinic reductase, which normally reduces folic acid to folinic acid. The antipurines, such as azathioprine, block the synthesis of ribonucleic acid by their antipurine action.

Medical conditions (apart from cancer) which have been treated with immunosuppressives include the 'minimal change' nephrotic syndrome, severe rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and Wegener's granulomatosis; all are conditions of unknown origin and the mechanism by which immunosuppressives act is still obscure, and although the reduction in circulating lymphocytes during treatment suggests that suppression of cell-mediated immunity is responsible, a completely different mechanism such as prevention of the proliferation of a viral agent cannot be excluded (Lessof, 1973).

Reports of the use of these drugs in cases of uveitis are reviewed in the paper by Dinning and Perkins in this issue (p. 397). It should be emphasized that all these reports concern small numbers of patients and in only one series was a double-blind controlled trial attempted, with inconclusive results. The report in this issue does support previous claims that some success has been achieved in Behçet's syndrome, and that in a proportion of cases remission has resulted and it has been possible to reduce previous high doses of corticosteroids. There is some evidence that chlorambucil produces fewer immediate toxic side-effects than other immunosuppressives, and it is mildly encouraging that no chromosomal damage was found in patients who had received only chlorambucil. Careful monitoring of the blood is essential to detect leucopenia or thrombocytopenia. It is the possible long-term effects of these drugs which are most worrying. Clearly they should not be used during pregnancy, and it is still uncertain whether they have a permanent effect on fertility. The most serious hazard is the risk of inducing tumours. Penn, Halgrimson, and Starzl (1971) reported an

incidence of tumours of 6 per cent in 236 patients with renal transplants treated with azathioprine and corticosteroids, compared with an incidence of 0.058 per cent in a general population of a similar age. Such long-term risks must be balanced against the short-term advantages in treating a non-fatal disease such as uveitis, and treatment can be justified only when there is a serious threat of blindness and

an unsatisfactory response to, or an intolerance of, adequate doses of steroids.

Until we have a better understanding of the aetiology of uveitis and the mechanism of action of immunosuppressives, their use will remain empirical and judgement of their effectiveness will rely on the accumulation of further clinical and experimental evidence.

References

- LESSOF, M. H. (1973) *Brit. J. Hosp. Med.*, **10**, 181
 PENN, I., HALGRIMSON, C. G., and STARZL, T. E. (1971) *Transplantation Proc.*, **3**, 773